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(54) Title: COMBINATION OF SEROTONIN REUPTAKE INHIBITORS AND NOREPINEPHRINE REUPTAKE INHIBITORS

(57) Abstract: This invention is directed in one embodiment to pharmaceutical compositions and methods for treating depression in a mammal. To a mammal in need of such treatment are administered: (i) at least one serotonin reuptake inhibitor or pharmaceutically acceptable salt thereof; and (ii) at least one norepinephrine reuptake inhibitor or pharmaceutically acceptable salt thereof, wherein the norepinephrine reuptake inhibitor is selected from the group consisting of Structure II, Structure III, and Structure IV as defined herein.



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**COMBINATION OF SEROTONIN REUPTAKE INHIBITORS AND NOREPINEPHRINE
REUPTAKE INHIBITORS**

BACKGROUND OF THE INVENTION

5 This invention is directed to a pharmaceutical compositions comprising a serotonin reuptake inhibitor or pharmaceutically acceptable salts thereof and a norepinephrine reuptake inhibitor or pharmaceutically acceptable salts thereof, and to methods of treatment with such a composition.

10 This invention is also directed to a pharmaceutical composition comprising a serotonin reuptake inhibitor or pharmaceutically acceptable salts thereof and optionally a norepinephrine reuptake inhibitor or pharmaceutically acceptable salts thereof, and to methods of treatment with such a composition, wherein the serotonin reuptake inhibitor is present in an amount sufficient for dopamine reuptake inhibition.

15 Serotonin plays a role in several psychiatric disorders, including anxiety, Alzheimer's disease, depression, nausea and vomiting, eating disorders, and migraine (see Rasmussen et al., "Chapter 1. Recent Progress in Serotonin (5HT)_{1A} Receptor Modulators", in Annual Reports in Medicinal Chemistry, Section I, 30, pp. 1-9, 1995, Academic Press, Inc.; Artigas et al., Trends Neurosci., 19 (9), 1996, pp. 378-383; and Wolf et al., Drug Development Research, 40, 1997, pp. 17-34). Serotonin also plays a role in both the positive and negative symptoms of schizophrenia, as discussed in Sharma et al., Psychiatric Annals., 26 (2), 20 February, 1996, pp. 88-92. Serotonin reuptake inhibitors, have been used to treat disorders or conditions such as depression, as described, for example, in WO 94/00047.

The antidepressant effect of norepinephrine reuptake inhibitors has been described, for example, in U.S. Patent No. 6,403,645.

25 The effect of combining selective serotonin reuptake inhibitors (SSRIs) in depressed patients with the norepinephrine reuptake inhibitor desipramine has been described in J.C. Nelson et al., Arch. Gen. Psychiatry, 39: 1419-1422, 1982; J.C. Nelson et al., Arch. Gen. Psychiatry, 48: 303-307, 1991; J.C. Nelson and L.H. Price, Am. J. Psychiatry, 152: 1538-1539, 1995; and M. Fava et al., Am. J. Psychiatry, 152: 1539, 1995. A combination of sertraline and of reboxetine has been described in Eur J Pharmacol, 1999, 364(2-3):123-32 and in J. Neural Transm., 2000, 107:1213-1227. A comparison of the stimulus properties of reboxetine and certain serotonin reuptake inhibitors has been described in Psychopharmacology 2001, 154:213-218. A combination of citalopram and of reboxetine has been described in WO 02/076461.

35 According to Brunswick et al., Am. J. Psychiatry, 2003, Vol. 160:10, pp. 1836-1841, dopamine transporter affinity may be higher than normal in the basal ganglia of depressed patients. Racemic reboxetine, a norepinephrine reuptake inhibitor, has been shown to affect the dopaminergic system preclinically, increasing dopamine in the prefrontal cortex. See

Sacchetti et al., Br. J. Pharmacol. 1999, Vol. 128, pp. 1332-1338; Page et al, Neuropsychopharmacology, 2002, Vol. 27, pp. 237-247; and Invernizzi et al., British J. of Pharmacology, 2001, Vol. 132, pp. 183-188.

5 However, citalopram, a serotonin reuptake inhibitor, does not show dopamine reuptake inhibition. Kugaya et al., Neuropsychopharmacology, 2003, Vol. 28, pp. 413-420. Similarly, the serotonin and norepinephrine reuptake inhibitor venlafaxine does not show dopamine reuptake inhibition (Marek et al, Society for Neuroscience Meeting, New Orleans, November 2003).

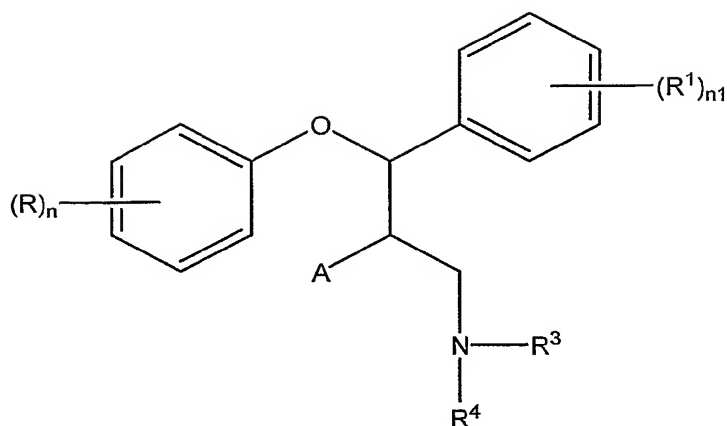
10 None of the previously published studies discloses or suggests a composition having a combined action of serotonin reuptake inhibition, norepinephrine reuptake inhibition, and dopamine reuptake inhibition in a dual component therapy, or methods of treatment with such a composition.

SUMMARY OF THE INVENTION

15 This invention is directed to a pharmaceutical composition for treating a disorder or condition selected from the group consisting of anxiety disorders, phobias, avoidant personality disorder, eating disorders, chemical dependencies, Parkinson's diseases, obsessive-compulsive disorder, negative symptoms of schizophrenia, cognitive dysfunction related to schizophrenia, premenstrual syndrome, stress-induced incontinence, headache, neuropathic pain, chronic pain, urinary incontinence, fibromyalgia, depression comorbid with
20 fibromyalgia, obesity, migraine, neuropathic pain associated with diabetes, affective symptoms of schizophrenia and a combination thereof in a mammal, the composition comprising: (i) at least one serotonin reuptake inhibitor or pharmaceutically acceptable salt thereof; (ii) at least one norepinephrine reuptake inhibitor or pharmaceutically acceptable salt thereof, wherein the at least one norepinephrine reuptake inhibitor is selected from the group
25 consisting of

(A) a compound having the formula of Structure II

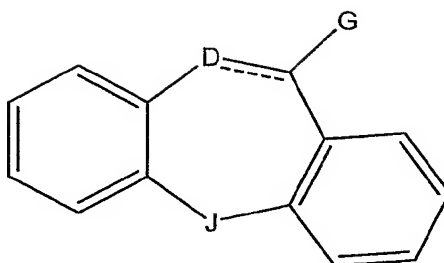
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Structure II

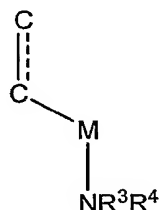
- wherein n and n_1 are, independently, 1, 2 or 3; each of the groups R and R^1 , which may be the same or different, is hydrogen; halogen; halo- C_1 - C_6 alkyl; hydroxy; C_1 - C_6 alkoxy; C_1 - C_6 alkyl optionally substituted with C_1 - C_6 alkyl or halogen; aryl- C_1 - C_6 alkyl optionally substituted with C_1 - C_6 alkyl or halogen; aryl- C_1 - C_6 alkoxy optionally substituted with C_1 - C_6 alkyl or halogen; $-\text{NO}_2$; $-\text{NR}^5\text{R}^6$ wherein R^5 and R^6 are, independently, hydrogen or C_1 - C_6 alkyl, or two adjacent R groups or two adjacent R^1 groups, taken together, form the $-\text{O}-\text{CH}_2-\text{O}-$ group;
- A is hydrogen or OR^2 ;
- R^2 is hydrogen; C_1 - C_{12} alkyl optionally substituted with C_1 - C_6 alkyl or halogen, or aryl-
 10 C_1 - C_6 alkyl;
- each of the groups R^3 and R^4 , which may be identical or different, is hydrogen, C_1 - C_6 alkyl optionally substituted with C_1 - C_6 alkyl or halogen, C_2 - C_4 alkenyl, C_2 - C_4 alkynyl, aryl- C_1 - C_4 alkyl optionally substituted with C_1 - C_6 alkyl or halogen, C_3 - C_7 cycloalkyl optionally substituted with C_1 - C_6 alkyl or halogen, or R^3 and R^4 with the nitrogen atom to which they are
 15 bound form a pentatomic or hexatomic saturated or unsaturated, optionally substituted with C_1 - C_6 alkyl or halogen, heteromonocyclic group optionally containing other heteroatoms selected from the group consisting of O, S and N;
- or R^2 and R^4 , taken together, form the $-\text{CH}_2-\text{CH}_2-$ group;
- (B) a compound having the formula of Structure III

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Structure III

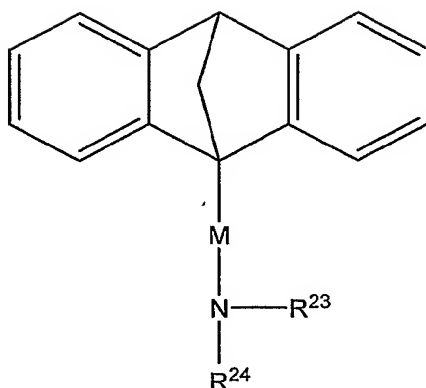
- wherein D is N or CR⁹, where R⁹ is hydrogen, C₁-C₆ alkyl optionally substituted with C₁-C₆ alkyl or halogen, C₂-C₄ alkenyl, C₂-C₄ alkynyl, aryl-C₁-C₄ alkyl optionally substituted with C₁-C₆ alkyl or halogen, or C₃-C₇ cycloalkyl optionally substituted with C₁-C₆ alkyl or halogen; G is NR⁷R⁸, wherein each of R⁷ and R⁸ is independently hydrogen, C₁-C₆ alkyl optionally substituted with C₁-C₆ alkyl or halogen, C₂-C₄ alkenyl, C₂-C₄ alkynyl, aryl-C₁-C₄ alkyl optionally substituted with C₁-C₆ alkyl or halogen, or C₃-C₇ cycloalkyl optionally substituted with C₁-C₆ alkyl or halogen; or R⁷ and R⁸ taken together with the nitrogen atom to which they are bound form a pentatomic or hexatomic, saturated or unsaturated, optionally substituted with C₁-C₆ alkyl or halogen heteromonocyclic group optionally containing one or more further additional heteroatoms selected from the group consisting of O, S and N; the bond between D and the ring carbon bonded to G is single or double; and J is O or L, where L is



- where the bond between the ring carbon of L and the carbon of L bonded to M is single or double; M is a C_n alkylene chain, where n is between 1 and 3; and each of R¹³ and R¹⁴ is independently hydrogen, C₁-C₆ alkyl optionally substituted with C₁-C₆ alkyl or halogen, C₂-C₄ alkenyl, C₂-C₄ alkynyl, aryl-C₁-C₄ alkyl optionally substituted with C₁-C₆ alkyl or halogen, C₃-C₇ cycloalkyl optionally substituted with C₁-C₆ alkyl or halogen, or R¹³ and R¹⁴ taken together with the nitrogen atom to which they are bound form a pentatomic or hexatomic, saturated or unsaturated, optionally substituted with C₁-C₆ alkyl or halogen heteromonocyclic group optionally containing one or more further additional heteroatoms selected from the group consisting of O, S and N; and

(C) a compound having the formula of Structure IV:

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Structure IV

- wherein M is a C_n alkylene chain, where n is between 1 and 3; and each of R²³ and R²⁴ is independently hydrogen, C₁-C₆ alkyl optionally substituted with C₁-C₆ alkyl or halogen, C₂-C₄ alkenyl, C₂-C₄ alkynyl, aryl-C₁-C₄ alkyl optionally substituted with C₁-C₆ alkyl or halogen, C₃-C₇ cycloalkyl optionally substituted with C₁-C₆ alkyl or halogen, or R²³ and R²⁴ taken together with the nitrogen atom to which they are bound form a pentatomic or hexatomic, saturated or unsaturated, optionally substituted with C₁-C₆ alkyl or halogen heteromonocyclic group optionally containing one or more further additional heteroatoms selected from the group consisting of O, S and N;
- and
- (iii) a pharmaceutically acceptable carrier.

This invention is also directed to:

- a method for treating a disorder or condition described in the previous paragraph in a mammal, the method comprising administering to a mammal in need of such treatment components (i) and (ii) described in the previous paragraph;
- the use of components (i) and (ii) described in the previous paragraph for preparing a medicament for treating a disorder or condition described in the previous paragraph in a mammal;
- a pharmaceutical composition for treating a disorder or condition that can be treated by enhancing serotonergic neurotransmission in a mammal, noradrenergic neurotransmission in a mammal, or a combination thereof, the composition comprising components (i), (ii) and (iii) described in the previous paragraph;
- a method for treating a disorder or condition that can be treated by enhancing serotonergic neurotransmission in a mammal, noradrenergic neurotransmission in a mammal, or a combination thereof, the method comprising administering to a mammal in need of such treatment components (i) and (ii) described in the previous paragraph;
- a pharmaceutical composition for treating depression in a mammal, the composition comprising components (i), (ii) and (iii) described in the previous paragraph;

a method for treating depression in a mammal, the method comprising administering to a mammal in need of such treatment components (i) and (ii) described in the previous paragraph; and

the use of components (i) and (ii) described in the previous paragraph for preparing a
5 medicament for treating depression in a mammal.

This invention is also directed to a composition for treating a disorder or condition described in the previous paragraphs in a mammal, the composition consisting essentially of components (i), (ii) and (iii) described in the previous paragraphs.

This invention is also directed to:

10 a composition comprising (i) at least one serotonin reuptake inhibitor or pharmaceutically acceptable salt thereof, wherein the at least one serotonin reuptake inhibitor is selected from the group consisting of sertraline, fluoxetine and fluvoxamine; and (ii) at least one norepinephrine reuptake inhibitor or pharmaceutically acceptable salt thereof, wherein the at least one norepinephrine reuptake inhibitor is selected from the group consisting of
15 racemic reboxetine, [S,S]-reboxetine, amoxapine, and maprotiline. The composition may be a composition for treating a disorder or condition selected from the group consisting of neuropathic pain, chronic pain, urinary incontinence, fibromyalgia, depression comorbid with fibromyalgia, obesity, migraine, neuropathic pain associated with diabetes, affective symptoms of schizophrenia and a combination thereof in a mammal; and

20 a composition consisting essentially of (i) at least one serotonin reuptake inhibitor or pharmaceutically acceptable salt thereof, wherein the at least one serotonin reuptake inhibitor is selected from the group consisting of sertraline, fluoxetine and fluvoxamine; and (ii) at least one norepinephrine reuptake inhibitor or pharmaceutically acceptable salt thereof, wherein the at least one norepinephrine reuptake inhibitor is selected from the group consisting of
25 racemic reboxetine, [S,S]-reboxetine, amoxapine, and maprotiline. The composition may be a composition for treating a disorder or condition selected from the group consisting of neuropathic pain, chronic pain, urinary incontinence, fibromyalgia, depression comorbid with fibromyalgia, obesity, migraine, neuropathic pain associated with diabetes, affective symptoms of schizophrenia and a combination thereof in a mammal.

30 The invention is also directed to:

a method for treating a disorder or condition described in the previous paragraphs in a mammal, the method comprising administering to a mammal in need of such treatment (i) at least one serotonin reuptake inhibitor or pharmaceutically acceptable salt thereof, wherein the at least one serotonin reuptake inhibitor is selected from the group consisting of sertraline,
35 fluoxetine and fluvoxamine; and (ii) at least one norepinephrine reuptake inhibitor or pharmaceutically acceptable salt thereof, wherein the at least one norepinephrine reuptake

inhibitor is selected from the group consisting of racemic reboxetine, [S,S]-reboxetine, amoxapine, and maprotiline; and

the use of components (i) and (ii) described in the previous paragraphs for preparing a medicament for treating a disorder or condition described in the previous paragraphs in a
5 mammal.

The invention is also directed to a composition comprising sertraline or a pharmaceutically acceptable salt thereof and [S,S]-reboxetine or a pharmaceutically acceptable salt thereof.

The invention is also directed to a composition for treating, for example, a disorder or
10 condition that can be treated by enhancing serotonergic neurotransmission in a mammal, dopaminergic transmission in a mammal, noradrenergic neurotransmission in a mammal, or a combination thereof, the composition comprising component (i) and optionally component (ii) described in the previous paragraphs, wherein component (i) is present in an amount sufficient for dopamine reuptake inhibition. Preferably, component (i) is sertraline or a
15 pharmaceutically acceptable salt thereof.

The invention is also directed to a method for treating a disorder or condition that can be treated by enhancing serotonergic neurotransmission in a mammal, dopaminergic transmission in a mammal, noradrenergic neurotransmission in a mammal, or a combination thereof, the method comprising administering to a mammal in need of such treatment
20 comprising component (i) and optionally component (ii) described in the previous paragraphs, wherein component (i) is present in an amount sufficient for dopamine reuptake inhibition. Preferably, component (i) is sertraline or a pharmaceutically acceptable salt thereof.

The invention is also directed to a composition comprising sertraline or a pharmaceutically acceptable salt thereof and optionally a norepinephrine reuptake inhibitor
25 selected from the group consisting of racemic reboxetine, [S,S]-reboxetine, amoxapine, and maprotiline, or pharmaceutically acceptable salts thereof, wherein sertraline or a pharmaceutically acceptable salt thereof is present in an amount sufficient for dopamine reuptake inhibition.

The invention is also directed to a composition comprising sertraline or a
30 pharmaceutically acceptable salt thereof and optionally [S,S]-reboxetine or a pharmaceutically acceptable salt thereof, wherein sertraline is present in an amount sufficient for dopamine reuptake inhibition.

In the method for treating a disorder or condition selected from the group consisting of anxiety disorders, phobias, avoidant personality disorder, eating disorders, chemical
35 dependencies, Parkinson's diseases, obsessive-compulsive disorder, negative symptoms of schizophrenia, premenstrual syndrome, stress-induced incontinence, headache, neuropathic pain, chronic pain, urinary incontinence, post-traumatic stress disorder, chronic stress, acute

stress, post-traumatic stress disorder, fibromyalgia, depression comorbid with fibromyalgia, obesity, the serotonin reuptake inhibitor may be sertraline present in an amount sufficient for dopamine reuptake inhibition. Similarly, in the composition for treating a disorder or condition as recited in this paragraph, the serotonin reuptake inhibitor may be sertraline present in an amount sufficient for dopamine reuptake inhibition. Similarly, in the method for treating a disorder or condition selected from the group consisting of neuropathic pain, chronic pain, urinary incontinence, post-traumatic stress disorder, chronic stress, acute stress, post-traumatic stress disorder, fibromyalgia, depression comorbid with fibromyalgia, obesity, the serotonin reuptake inhibitor may be sertraline present in an amount sufficient for dopamine reuptake inhibition.

In the method for treating depression, the serotonin reuptake inhibitor may be sertraline or a pharmaceutically salt thereof present in an amount sufficient for dopamine reuptake inhibition. In one embodiment, the serotonin reuptake inhibitor is sertraline or a pharmaceutically acceptable salt thereof, and the norepinephrine reuptake inhibitor is [S,S]-reboxetine or a pharmaceutically acceptable salt thereof, wherein sertraline is present in an amount sufficient for dopamine reuptake inhibition, wherein the amount of sertraline is from about 150 mg to about 200 mg.

Similarly, in the composition for treating depression, the serotonin reuptake inhibitor may be sertraline present in an amount sufficient for dopamine reuptake inhibition. In one embodiment, the serotonin reuptake inhibitor is sertraline or a pharmaceutically acceptable salt thereof, and the norepinephrine reuptake inhibitor is [S,S]-reboxetine or a pharmaceutically acceptable salt thereof, wherein sertraline is present in an amount sufficient for dopamine reuptake inhibition, wherein the amount of sertraline is from about 150 mg to about 200 mg.

In the composition comprising (i) at least one serotonin reuptake inhibitor or pharmaceutically acceptable salt thereof, wherein the at least one serotonin reuptake inhibitor is selected from the group consisting of sertraline, fluoxetine and fluvoxamine; and (ii) at least one norepinephrine reuptake inhibitor or pharmaceutically acceptable salt thereof, wherein the at least one norepinephrine reuptake inhibitor is selected from the group consisting of racemic reboxetine, [S,S]-reboxetine, amoxapine, and maprotiline, the serotonin reuptake inhibitor may be sertraline present in an amount sufficient for dopamine reuptake inhibition. Similarly, in the composition consisting essentially of (i) at least one serotonin reuptake inhibitor or pharmaceutically acceptable salt thereof, wherein the at least one serotonin reuptake inhibitor is selected from the group consisting of sertraline, fluoxetine and fluvoxamine; and (ii) at least one norepinephrine reuptake inhibitor or pharmaceutically acceptable salt thereof, wherein the at least one norepinephrine reuptake inhibitor is selected from the group consisting of racemic reboxetine, [S,S]-reboxetine, amoxapine, and

maprotiline, the serotonin reuptake inhibitor may be sertraline present in an amount sufficient for dopamine reuptake inhibition.

The pharmaceutical compositions and methods of this invention may also be used for preventing a relapse in a disorder or condition described in the previous paragraphs by administering to a mammal in need of such prevention components (i) and (ii) of the composition. The pharmaceutical compositions and methods of this invention may further be used for treating a symptom associated with a disorder or condition described in the previous paragraphs, wherein the symptom is selected from the group consisting of cognitive dysfunctions and somatic complaints.

"Enhancing serotonergic neurotransmission," as used herein, refers to increasing or improving the neuronal process whereby the monoamine serotonin is released by a pre-synaptic cell upon excitation and crosses the synapse to stimulate or inhibit the post-synaptic cell. "Enhancing dopaminergic neurotransmission," as used herein, refers to increasing or improving the neuronal process whereby the monoamine dopamine is released by a pre-synaptic cell upon excitation and crosses the synapse to stimulate or inhibit the post-synaptic cell. "Enhancing noradrenergic neurotransmission," as used herein, refers to increasing or improving the neuronal process whereby the monoamine norepinephrine is released by a pre-synaptic cell upon excitation and crosses the synapse to stimulate or inhibit the post-synaptic cell.

"Chemical dependency," as used herein, means an abnormal craving or desire for, or an addiction to a drug. Such drugs are generally administered to the affected individual by any of a variety of means of administration, including oral, parenteral, nasal or by inhalation. "Treating a chemical dependency," as used herein, means reducing or alleviating such dependency.

A "unit dosage form" as used herein is any form that contains a unit dose of the serotonin reuptake inhibitor or a pharmaceutically acceptable salt thereof, of the norepinephrine reuptake inhibitor or a pharmaceutically acceptable salt thereof, or of the serotonin reuptake inhibitor or pharmaceutically acceptable salt thereof and the norepinephrine reuptake inhibitor or pharmaceutically acceptable salt thereof. A unit dosage form may be, for example, a tablet or a capsule. The unit dosage form may also be in liquid form, such as a solution or suspension.

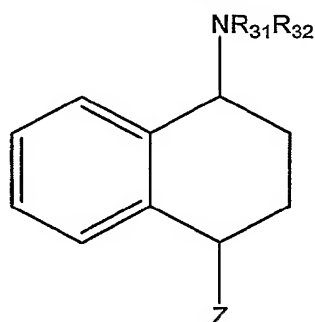
A "serotonin reuptake inhibitor" as used herein is a reuptake inhibitor of the monoamine serotonin. For example, the serotonin reuptake inhibitor may be a selective serotonin reuptake inhibitor (SSRI). The serotonin reuptake inhibitor may have additional pharmacological properties, for example, antagonism of 5-HT_{1A} or 5-HT_{2A/C} receptors, or partial inhibition of a norepinephrine transporter (NET). At or above certain doses, as described further herein, the serotonin reuptake inhibitor shows dopamine reuptake inhibition.

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"An amount sufficient for dopamine reuptake inhibition" is intended to refer to an amount that is sufficient to displace at least about 15% β -CIT from the dopamine transporter as assessed by SPECT imaging.

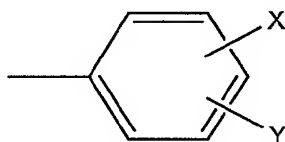
Exemplary selective serotonin reuptake inhibitors (SSRI) which may be used in accordance with this invention include those having structure I shown below:

Structure I



or a pharmaceutically acceptable salt thereof,

wherein R_{31} is selected from the group consisting of hydrogen and normal alkyl of from 1 to 3 carbon atoms, R_{32} is normal alkyl of from 1 to 3 carbon atoms, Z is



X and Y are each selected from the group consisting of hydrogen, fluoro, chloro, bromo, trifluoromethyl, alkoxy of from 1 to 3 carbon atoms and cyano, with at least one of X and Y being other than hydrogen,

W is selected from the group consisting of hydrogen, fluoro, chloro, bromo, trifluoromethyl and alkoxy of from 1 to 3 carbon atoms,

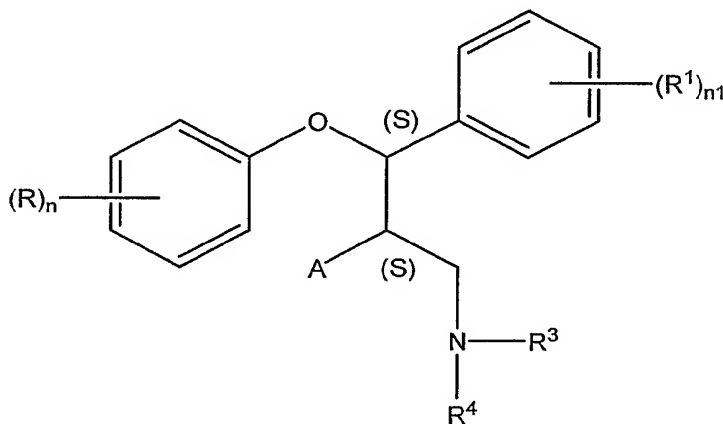
and $NR_{31}R_{32}$ and Z have a cis relationship.

An exemplary compound of Structure I is sertraline, (1S-*cis*)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthalenamine, which may be prepared as described in U.S. Pat. No. 4,536,518. SSRI that may be used in accordance with this invention also include, but are not limited to: femoxetine, which may be prepared as described in U.S. Pat. No. 3,912,743; fluoxetine, which may be prepared as described in U.S. Pat. No. 4,314,081; fluvoxamine, which may be prepared as described in U.S. Pat. No. 4,085,225; indalpine, which may be prepared as described in U.S. Pat. No. 4,064,255; indeloxazine, which may be prepared as described in U.S. Pat. No. 4,109,088; milnacipran, which may be prepared as described in U.S. Pat. No. 4,478,836; paroxetine, which may be prepared as described in U.S. Pat. No. 3,912,743 or U.S. Pat. No. 4,007,196; sibutramine, which may be prepared as

described in U.S. Pat. No. 4,929,629; zimeldine, which may be prepared as described in U.S. Pat. No. 3,928,369; citalopram; escitalopram; fenfluramine; venlafaxine and duloxetine.

A "norepinephrine reuptake inhibitor" as used herein is a reuptake inhibitor of the monoamine norepinephrine. For example, the norepinephrine reuptake inhibitor may be a selective norepinephrine reuptake inhibitor. As another example, the norepinephrine reuptake inhibitor may have additional pharmacological properties, for example, antagonism of 5-HT₂ receptors. As another example, the norepinephrine reuptake inhibitor may affect the dopaminergic transport system, for example, through the intermediacy of NET. Norepinephrine reuptake inhibition is readily determined by those skilled in the art according to standard assays. As an example, norepinephrine reuptake inhibitors which may be used in accordance with this invention include compounds having structure II defined above, or a pharmaceutically acceptable salt thereof. As another example, norepinephrine reuptake inhibitors which may be used in accordance with this invention include compounds having structure III defined above, or a pharmaceutically acceptable salt thereof. As another example, norepinephrine reuptake inhibitors which may be used in accordance with this invention include compounds having structure IV defined above, or a pharmaceutically acceptable salt thereof.

In an exemplary embodiment of the invention, the norepinephrine reuptake inhibitor is the [S,S]-enantiomer of Structure II, shown as Structure II' below, where A = OR² and R, R¹, R², R³, R⁴, n and n1 are as defined in Structure II:



Structure II

For example, the norepinephrine reuptake inhibitor of Structure II' may be [S,S]-reboxetine, which is described in British patent GB 2,167,407, U.S. Patent Application No. 20020061910, U.S. Patent No. 6,465,458.

In another exemplary embodiment of the invention, the norepinephrine reuptake inhibitor of Structure II is atomoxetine or racemic reboxetine.

In another exemplary embodiment of the invention, the norepinephrine reuptake inhibitor of Structure III is amoxapine, nortriptyline, or protriptyline.

In another exemplary embodiment of the invention, the norepinephrine reuptake inhibitor of Structure IV is maprotiline.

5 In one exemplary embodiment of the composition of the invention, the composition comprises a norepinephrine reuptake inhibitor having Structure II', and sertraline as the serotonin reuptake inhibitor.

In another exemplary embodiment of the invention, the composition comprises sertraline as the serotonin reuptake inhibitor and [S,S]-reboxetine as the norepinephrine
10 reuptake inhibitor.

In another exemplary embodiment of the invention, the composition consists essentially of sertraline as the serotonin reuptake inhibitor and [S,S]-reboxetine as the norepinephrine reuptake inhibitor.

The combination of a norepinephrine reuptake inhibitor or a pharmaceutically
15 acceptable salt thereof and a serotonin reuptake inhibitor or pharmaceutically acceptable salt thereof is also referred to herein as "the active combination." The term "the active combination" may also be used to denote the combination of a norepinephrine reuptake inhibitor or a pharmaceutically acceptable salt thereof and a serotonin reuptake inhibitor or
20 pharmaceutically acceptable salt thereof wherein the serotonin reuptake inhibitor or pharmaceutically acceptable salt also inhibits dopamine reuptake. The active combination is a useful psychotherapeutic and may be used in the treatment of the disorders or conditions described herein. Examples of the disorders or conditions which may be treated by the methods and compositions of this invention are as follows:

depression, including, for example, depression in cancer patients, depression in
25 Parkinson's patients, Postmyocardial Infarction depression, depression in patients with human immunodeficiency virus (HIV), Subsyndromal Symptomatic depression, depression in infertile women, pediatric depression, major depression, single episode depression, recurrent depression, child abuse induced depression, post partum depression, DSM-IV major depression, treatment-refractory major depression, severe depression, psychotic depression,
30 post-stroke depression, neuropathic pain, manic depressive illness, including manic depressive illness with mixed episodes and manic depressive illness with depressive episodes, seasonal affective disorder, bipolar depression BP I, bipolar depression BP II, melancholy, or major depression with dysthymia; dysthymia; anxiety disorders, including, for example, generalized anxiety disorder, panic disorder, PTSD, and social anxiety disorder;
35 phobias, including, for example, agoraphobia, social phobia or simple phobias; eating disorders, including, for example, anorexia nervosa or bulimia nervosa; chemical dependencies, including, for example, addictions to alcohol, cocaine, amphetamine and other

psychostimulants, morphine, heroin and other opioid agonists, phenobarbital and other barbiturates, nicotine, diazepam, benzodiazepines and other psychoactive substances; Parkinson's diseases, including, for example, dementia in Parkinson's disease, neuroleptic-induced parkinsonism or tardive dyskinesias; and headache, including, for example,
5 headache associated with vascular disorders.

Disorders or conditions that may be treated by the composition and method of the present invention also include withdrawal syndrome; adjustment disorders, including depressed mood, mixed anxiety and depressed mood, disturbance of conduct, and mixed disturbance of conduct and depressed mood; age-associated learning and mental disorders,
10 including Alzheimer's disease; apathy; attention-deficit disorders, or other cognitive disorders, due to general medical conditions; attention-deficit hyperactivity disorder (ADHD); bipolar disorder; chronic fatigue syndrome; chronic or acute stress; conduct disorder; cyclothymic disorder; somatoform disorders such as somatization disorder, conversion disorder, pain disorder, hypochondriasis, body dysmorphic disorder, undifferentiated disorder, and
15 somatoform NOS; incontinence; inhalation disorders; intoxication disorders; mania; oppositional defiant disorder; peripheral neuropathy; post-traumatic stress disorder; late luteal phase dysphoric disorder; psychotic disorders including schizoaffective disorders; sleep disorders, including narcolepsy and enuresis; specific developmental disorders; SSRI "poop out" syndrome, or a patient's failure to maintain a satisfactory response to SSRI therapy after
20 an initial period of satisfactory response; and tic disorders including Tourette's disease.

As an example, the mammal in need of the treatment or prevention may be a human. As another example, the mammal in need of the treatment or prevention may be a mammal other than a human.

A norepinephrine reuptake inhibitor and a serotonin reuptake inhibitor, each of which
25 is used in formulating the pharmaceutical composition of this invention, are each referred to herein as an "active compound." An active compound which is basic in nature is capable of forming a wide variety of different salts with various inorganic and organic acids. The acid addition salts are readily prepared by treating the base compounds with a substantially equivalent amount of the chosen mineral or organic acid in an aqueous solvent medium or in
30 a suitable organic solvent such as methanol or ethanol. Upon careful evaporation of the solvent, the desired solid salt is obtained.

The acids which are used to prepare the pharmaceutically acceptable acid salts of the active compounds used in formulating the pharmaceutical compositions of this invention that are basic in nature are those which form non-toxic acid addition salts, i.e., salts
35 containing pharmacologically acceptable anions. Non-limiting examples of the salts include the acetate, benzoate, β -hydroxybutyrate, bisulfate, bisulfite, bromide, butyne-1,4-dioate, carpoate, chloride, chlorobenzoate, citrate, dihydrogenphosphate, dinitrobenzoate, fumarate,

glycollate, heptanoate, hexyne-1,6-dioate, hydroxybenzoate, iodide, lactate, maleate, malonate, mandelate, metaphosphate, methanesulfonate, methoxybenzoate, methylbenzoate, monohydrogenphosphate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, oxalate, phenylbutyrate, phenylproionate, phosphate, phthalate, phylacetate, 5 propanesulfonate, propiolate, propionate, pyrophosphate, pyrosulfate, sebacate, suberate, succinate, sulfate, sulfite, sulfonate, tartrate, xylenesulfonate, acid phosphate, acid citrate, bitartrate, succinate, gluconate, saccharate, nitrate, methanesulfonate and pamoate [i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)] salts. For the norepinephrine reuptake inhibitors, such as reboxetine and [S,S]-reboxetine, advantageous examples include the fumarate, 10 succinate, citrate and tartrate salts.

DETAILED DESCRIPTION OF THE INVENTION

The norepinephrine reuptake inhibitors and serotonin reuptake inhibitors, which may also show dopamine reuptake inhibition as described herein, that are used in formulating the pharmaceutical compositions of this invention are preferably administered together in a 15 pharmaceutical composition. For example, compositions containing the serotonin reuptake inhibitors and the norepinephrine reuptake inhibitors can be administered as solutions in a volume of 1 ml/kg. The vehicle used is varied depending on the solubility of the serotonin reuptake inhibitor and of the norepinephrine reuptake inhibitor used.

The norepinephrine reuptake inhibitors and the serotonin reuptake inhibitors, which 20 may also show dopamine reuptake inhibition as described herein, that are used in formulating the pharmaceutical compositions of this invention may advantageously be used in conjunction with other therapeutic agents which do not appreciably block serotonin uptake or affect monoamine oxidase, such as mirtazapine, mianserin, bupropion, lithium salts, antiepileptic drugs such as carbamazepine, valproate, lamotrigine, topiramate, gabapentin, pregabalin, with 25 atypical antipsychotic drugs such as olanzapine, risperidone, quetiapine, ziprasidone and aripiprazole, and/or with antiparkinsonian agents such as dopaminergic antiparkinsonian agents such as levodopa, preferably in combination with a peripheral decarboxylase inhibitor such as benserazide or carbidopa. As another example, the norepinephrine reuptake inhibitor and the serotonin reuptake inhibitor, which may also show dopamine reuptake 30 inhibition as described herein, that are used in formulating the pharmaceutical composition of this invention may advantageously be used in combination with a 5-HT_{1B} antagonist. An exemplary is elzasonan or a pharmaceutically acceptable salt thereof. For example, elzasonan may be present in amounts such as about 0.1 to about 200 mg, for example about 0.1 mg to about 50 mg, as another example from about 0.1 mg to about 20 mg, as another 35 example from about 0.1 mg to about 10 mg, as another example from about 0.1 mg to about 5 mg. The methods of treatment of the invention likewise may include treatment of a disorder

or condition with a norepinephrine reuptake inhibitor, a serotonin reuptake inhibitor, and a 5-HT1B antagonist such as elzasonan.

It is to be understood that the present invention covers the use of a serotonin reuptake inhibitor or a pharmaceutically acceptable salt thereof and a norepinephrine reuptake inhibitor or pharmaceutically acceptable salt thereof in combination with one or more other therapeutic agents.

Activity of the active combinations as antidepressants and related pharmacological properties can be determined by methods (1)-(3) below, which are described in Koe, B. et al. Journal of Pharmacology and Experimental Therapeutics, 226 (3), 686-700 (1983). Specifically, activity can be determined by studying (1) their ability to affect the efforts of mice to escape from a swim-tank by the Porsolt mouse "behavior despair" test, (2) their ability to potentiate 5-hydroxytryptophan-induced behavioral symptoms in mice in vivo, and (3) their ability to block the uptake of serotonin, norepinephrine, dopamine or a combination thereof by synaptosomal rat brain cells in vitro. The ability of the active combinations to counteract reserpine hypothermia in mice in vivo can be determined according to the methods described in U.S. Pat. No. 4,029,731. The activity of the active combinations as antidepressants and related pharmacological properties also can be determined by methods (4)-(8) below. Specifically, activity can be determined by studying (4) their ability to reverse the stress-induced decrease in sucrose intake in rodents described in Papp, M. et al., European Journal of Pharmacology, 261, 141-147 (1994), (5) learned helplessness paradigm described in Martin P et al., Life Sciences, 48, 2505-2511 (1991), (6) reversing the behavioral deficits of olfactory bulbectomized rats described in Broekkamp CL et al., Pharmacology, Biochemistry and Behavior, 13, 643-646 (1980), (7) increasing down-regulation or desensitization of beta-adrenergic receptors described in Mishra R. et al., Neuropharmacology, 19, 983-987 (1980), and (8) increasing extracellular levels of serotonin, norepinephrine, and/or dopamine in the prefrontal cortex of freely-moving rodents by in vivo dialysis described in Millan MJ et al., European Journal of Neuroscience, 12, 1079-1095 (2000).

Activity of the active combinations in the treatment of anxiety may be determined from lactate-induced panic-like responses in panic-prone rats as described in Shekhar, A. and Keim S.R., J. Neurosci, 1997, 17:9726-9735, and Shekhar, A. and Keim, S.R., Neuropharmacol., 2000, 39:1139-1146. Activity of the active combinations in the treatment of anxiety may also be determined from anxiety screens such as those that include various derivations of conflict models or punishment models in rodents as described by J.L. Howard and G.T. Pollard in Psychopharmacology of Anxiolytics and Antidepressants, (ED) SE File (1991), Pergamon press Inc. (New York), pp. 131-153.

The pharmaceutical compositions described, herein may be prescription pharmaceutical compositions or over-the-counter pharmaceutical compositions. As used

herein, a "prescription pharmaceutical composition" is a composition which is effective to deliver an active compound to a human as prescribed by a physician. An "over-the-counter pharmaceutical composition" is a composition which is effective to deliver an active compound to a human which does not require a prescription from a physician in order to be administered to the human.

The pharmaceutical compositions described herein may be formulated in a conventional manner using one or more pharmaceutically acceptable carriers. Thus, the active combinations of this invention may be formulated for oral, buccal, intranasal, parenteral (for example, intravenous, intramuscular or subcutaneous), sublingual or rectal administration, or may be in the form of a patch, or in a form suitable for administration by inhalation or insufflation, and may be administered orally, buccally, intranasally, parenterally (for example, intravenously, intramuscularly or subcutaneously) or rectally or by inhalation or insufflation.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents, including pregelatinized maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose; fillers, including lactose, microcrystalline cellulose or calcium phosphate; lubricants, including magnesium stearate, talc or silica; disintegrants, including potato starch or sodium starch glycolate; or wetting agents, including sodium lauryl sulphate. The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents, including sorbitol syrup, methyl cellulose or hydrogenated edible fats; emulsifying agents, including lecithin or acacia, non-aqueous vehicles, including almond oil, oily esters or ethyl alcohol; and preservatives, including methyl or propyl p-hydroxybenzoates or sorbic acid.

For buccal administration, the composition may take the form of tablets or lozenges formulated in conventional manner.

The active compounds used in formulating the pharmaceutical composition of this invention may be formulated for parenteral administration by injection, including using conventional catheterization techniques or infusion. Formulations for injection may be presented in unit dosage form, for example, in ampoules or in multi-dose containers, with an added preservative.

The compositions containing the active compounds may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulating agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active

ingredient may be in powder form for reconstitution with a suitable vehicle, for example, sterile pyrogen-free water, before use.

The active compounds used in formulating the pharmaceutical composition of this invention may also be formulated in rectal compositions such as suppositories or retention
5 enemas, for example, containing conventional suppository bases such as cocoa butter or other glycerides.

For intranasal administration or administration by inhalation, the active compounds used in formulating the pharmaceutical compositions of this invention are conveniently delivered in the form of a solution or suspension from a pump spray container that is
10 squeezed or pumped by the patient or as an aerosol spray presentation from a pressurized container or a nebulizer, with the use of a suitable propellant, for example, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the unit dose may be determined by providing a valve to deliver a metered amount. The pressurized container or nebulizer may
15 contain a solution or suspension of the active compounds. Capsules and cartridges, made, for example, from gelatin, for use in an inhaler or insufflator may be formulated containing a powder mix of a compound of this invention and a suitable powder base such as lactose or starch.

The norepinephrine reuptake inhibitors and the serotonin reuptake inhibitors used in
20 formulating the pharmaceutical compositions of this invention may be administered alone or preferably together with pharmaceutically acceptable carriers by any of the routes previously indicated, and such administration may be carried out in both single and multiple doses. More particularly, the active combination can be administered in a wide variety of different dosage forms, i.e., the active combination may be combined with various pharmaceutically-
25 acceptable inert carriers in the form of tablets, capsules, lozenges, troches, hard candies, powders, sprays, aqueous suspension, injectable solutions, elixirs, syrups, and the like. Such carriers include solid diluents or fillers, sterile aqueous media and various non-toxic organic solvents, etc. Moreover, oral pharmaceutical formulations containing the active combination may be suitably sweetened and/or flavored by means of various agents of the type commonly
30 employed for such purposes.

The amounts of a) the serotonin reuptake inhibitor or pharmaceutically acceptable salt thereof, and b) the norepinephrine reuptake inhibitor or pharmaceutically acceptable salt thereof are preferably amounts such that the combination of a) and b) is effective in treating the disorder or condition. The amount of the serotonin reuptake inhibitor or pharmaceutically
35 acceptable salt thereof is preferably an amount effective in enhancing serotonergic neurotransmission in a mammal. The amount of the norepinephrine reuptake inhibitor or pharmaceutically acceptable salt thereof is preferably an amount effective in enhancing

noradrenergic neurotransmission in a mammal. In one preferred embodiment, the amount of the serotonin reuptake inhibitor is an amount sufficient for dopamine reuptake inhibition. Affinity for the sertraline transporter (SERT) and for DAT transporter is determined by the amount of the β -CIT ligand that is displaced. The extent of dopamine reuptake inhibition, measured by transporter displacement using β -CIT in combination with extracellular dopamine increase, is greater than the extent of placebo.

The pharmaceutical compositions of the inventions achieve occupancy of the serotonin transporter and of the norepinephrine transporter by combining a serotonin reuptake inhibitor or pharmaceutically acceptable salt thereof with a norepinephrine reuptake inhibitor or pharmaceutically acceptable salt thereof. In one exemplary embodiment of the invention, the serotonin reuptake inhibitor or pharmaceutically acceptable salt thereof may be present in an amount sufficient to displace at least about 45% β -CIT from the serotonin transporter as assessed by SPECT imaging. The norepinephrine reuptake inhibitor or pharmaceutically acceptable salt thereof may be present in an amount such that the norepinephrine transporter has at least 50% occupancy, as an example at least 75% occupancy, as another example between 75% and 90% occupancy, as another example at least 90% occupancy, as another example between 90% and 100% occupancy, including 100% occupancy. In an exemplary embodiment, at least 75% occupancy of the norepinephrine transporter is maintained until the administration of a successive unit dose or unit dosage form of the composition of the invention. As used herein, "occupancy of the norepinephrine transporter" is intended to refer to occupancy of all norepinephrine transporters. Similarly, for example, "at least 75% occupancy" of the norepinephrine transporter is intended to mean that all norepinephrine transporters have an occupancy of at least 75%. Similarly, as another example, "at least 90% occupancy" of the norepinephrine transporter is intended to mean that all norepinephrine transporters have an occupancy of at least 90%. Similarly, as used herein, "an amount sufficient to displace at least about 45% β -CIT from the serotonin transporter" is an amount sufficient to displace at least about 45% β -CIT from all serotonin transporters.

In another embodiment of the invention, the serotonin reuptake inhibitor is present in an amount sufficient for dopamine reuptake inhibition. An amount sufficient for dopamine reuptake inhibition is an amount sufficient to displace at least about 15% β -CIT from the dopamine transporter, wherein "an amount sufficient to displace at least about 15% β -CIT from the dopamine transporter" is intended to mean an amount sufficient to displace at least about 15% β -CIT from all dopamine transporters. For example, the amount sufficient for dopamine reuptake inhibition may be an amount sufficient to displace about 15%, 16%, 17%, 18%, 19%, 20%, 21%, 22%, 23%, 24%, 25%, 26%, 27%, 28%, 29%, 30%, 31%, 32%, 33%, 34%, 35%, 36%, 37%, 38%, 39%, and 40% β -CIT from the dopamine transporter. When

sertraline is used as the serotonin reuptake inhibitor, the amount sufficient to displace at least about 15% β -CIT from the dopamine transporter is about 150 mg.

Binding data are shown in Tables 1 – 3 herein. During periods 1, 2, and 3, there were statistically significant differences among the treatment groups for each brain site shown in the tables ($p \leq 0.040$). For midbrain and diencephalon, the mean [123 I] β -CIT binding for sertraline 25 mg and sertraline 50 mg were significantly less than for placebo. For striatum, the mean [123 I] β -CIT binding for sertraline 25 mg and sertraline 50 mg were significantly greater than for placebo. There were no statistically significant period or carryover effects ($p \geq 0.052$). The comparisons of the treatments during successive randomization periods 1, 2, and 3 are summarized in Table 1 below.

Table 1: Summary of Analysis of [123 I] β -CIT Binding for Periods 1, 2, and 3

Site	Treatment Test	Reference	Means (LS means)			90% Confidence Limits	
			Test	Reference	Difference	Lower	Upper
Midbrain	Sertraline 25 mg	Placebo	0.91	1.49	-0.58	-1.03	-0.13
	Sertraline 50 mg	Placebo	0.60	1.49	-0.89	-1.34	-0.45
Diencephalon	Sertraline 25 mg	Placebo	1.91	3.42	-1.51	-2.23	-0.80
	Sertraline 50 mg	Placebo	1.58	3.42	-1.84	-2.56	-1.13
Striatum	Sertraline 25 mg	Placebo	10.06	9.44	0.62	0.26	0.98
	Sertraline 50 mg	Placebo	9.83	9.44	0.39	0.03	0.75

For the comparison of periods 1, 2, 3, and 4, there were statistically significant differences among the treatment groups for each site ($p \leq 0.007$). For midbrain and diencephalon, the mean [123 I] β -CIT binding for sertraline 25 mg, sertraline 50 mg, and sertraline 150 mg were significantly less than for placebo. For striatum, the mean [123 I] β -CIT binding for sertraline 150 mg was significantly less than for placebo. The Least Square Means for sertraline 25 mg and sertraline 50 mg were greater than the mean for placebo but these differences were not statistically significant. The comparisons of the treatments during successive randomization periods 1, 2, 3, and 4 are summarized in Table 2 below.

Table 2: Summary of Analysis of [¹²³I] β-CIT Binding for Periods 1, 2, 3, and 4

Site	Treatment		Means (LS means)			90% Confidence Limits	
	Test	Reference	Test	Reference	Difference	Lower	Upper
Midbrain	Sertraline	Placebo	0.93	1.45	-0.52	-0.84	-0.20
	25 mg						
	Sertraline	Placebo	0.63	1.45	-0.82	-1.14	-0.50
	50 mg						
Diencephalon	Sertraline	Placebo	0.77	1.45	-0.68	-0.99	-0.36
	150 mg						
	Sertraline	Placebo	1.88	3.23	-1.35	-1.97	-0.72
	25 mg						
Striatum	Sertraline	Placebo	1.80	3.23	-1.43	-2.05	-0.80
	50 mg						
	Sertraline	Placebo	1.62	3.23	-1.60	-2.23	-0.98
	150 mg						
Striatum	Sertraline	Placebo	10.04	9.32	0.72	-0.16	1.60
	25 mg						
	Sertraline	Placebo	9.97	9.32	0.64	-0.23	1.52
	50 mg						
Striatum	Sertraline	Placebo	8.17	9.32	-1.15	-2.03	-0.28
	150 mg						

Table 3 shows the mean binding and mean percent displacement for [¹²³I] β-CIT in the midbrain, diencephalon, and striatum based on images collected with the Prism-XP camera. These data show that sertraline at 150 mg binds to the dopamine transporter.

Table 3 - Mean Binding and Mean Percent Displacement of [¹²³I] β-CIT for Midbrain, Diencephalon, and Striatum Based on images collected with the Prism-XP camera

		No. of subjects =6					
				Sertraline			
		Baseline	Placebo	25 mg	50 mg	150 mg	
Midbrain							
Mean ±SD		1.65 ± 0.39	1.45 ± 0.38	0.93 ± 0.64	0.63 ± 0.36	0.77 ± 0.31	
Mean	Percent	--	--	-46.06	± -61.17	± -53.69	±
Displacement ±SD				26.72	24.78	10.89	

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		No. of subjects =6					
		Baseline	Placebo	Sertraline			
				25 mg	50 mg	150 mg	
Diencephalon							
Mean ±SD		3.28 ± 0.96	3.23 ± 1.2	1.88 ± 1.4	1.8 ± 0.45	1.62 ± 0.71	
Mean	Percent	--	--	-46.29	± -44.12	± -49.41	±
Dispacement ±SD				23.97	9.23	16.02	
Striatum							
Mean ±SD		9.79 ± 3.48	9.32 ± 3.48	10.04 ± 3.85	9.97 ± 3.3	8.17 ± 2.66	
Mean	Percent	--	--	2.4 ± 6.81	2.66 ± 7.4	-15.27 ±	
Dispacement ±SD						14.5	
Baseline = Value on Day 0. The displacement percentages are based on the baseline values							

Baseline = Value on Day 0. The displacement percentages are based on the baseline values

An exemplary daily dose of a serotonin reuptake inhibitor in a pharmaceutical composition of this invention for oral, parenteral, rectal or buccal administration to the average adult human for the treatment of the conditions referred to above is from about 1mg to 300 mg of serotonin reuptake inhibitor per unit dose administered 1 to 3 times per day, such as 25mg to about 300mg of sertraline, preferably from about 50mg to about 200mg of sertraline per unit dose which could be administered, for example, 1 to 3 times per day, or such as about 5 mg to about 80 mg of fluoxetine per unit dose, preferably from about 10 mg to about 40 mg of fluoxetine per unit dose which could be administered, for example, 1 to 3 times per day, or such as about 50 mg to about 300 mg of fluvoxamine per unit dose, preferably 100 mg to 200 mg of fluvoxamine per unit dose, which could be administered, for example, 1 to 3 times per day, or such as about 5 mg to about 30 mg of escitalopram, preferably about 10 mg to about 20 mg of escitalopram, which could be administered, for example, 1 to 3 times per day, or such as about 10 mg to about 60 mg of citalopram, preferably about 20 mg to about 40 mg of citalopram, which could be administered, for example, 1 to 3 times per day, or such as about 10 to about 50 mg of paroxetine, preferably about 10 mg to about 40 mg of paroxetine, which could be administered, for example, 1 to 3 times per day.

An exemplary daily dose of a serotonin reuptake inhibitor in a pharmaceutical composition of this invention for oral, parenteral, rectal or buccal administration to the average adult human for the treatment of the conditions referred to above, wherein the dose is sufficient for dopamine reuptake inhibition, is 150 mg or more of the serotonin reuptake inhibitor per unit dose per day. If sertraline is used as the serotonin reuptake inhibitor, amounts of about 150, 160, 170, 180, 190, 200, 210, 220, 230, 240, 250, 260, 270, 280, 290, 300, 310, 320, 330, 340, and 350 mg per unit dose per day are exemplary amounts that are sufficient for dopamine reuptake inhibition. As additional examples, the amount of sertraline

sufficient for dopamine reuptake inhibition may range from about 150 mg to about 350 mg; about 150 mg to about 200 mg; from about 170 mg to about 340 mg; from about 190 mg to about 330 mg; from about 200 mg to about 310 mg; from about 210 mg to about 300 mg; from about 220 mg to about 290 mg; from about 230 mg to about 280 mg; from about 240 mg to about 270 mg; from about 240 mg to about 250 mg; from about 250 mg to about 260 mg; from about 260 mg to about 270 mg; from about 270 mg to about 280 mg; from about 280 mg to about 290 mg; and from about 290 mg to about 300 mg.

An exemplary daily dose of the norepinephrine reuptake inhibitor in a pharmaceutical composition of this invention for oral, parenteral, rectal or buccal administration to the average adult human for the treatment of the conditions referred to above is from about 1 to 300 mg of norepinephrine reuptake inhibitor per unit dose, such as about 1mg to about 30 mg of racemic reboxetine, preferably from about 4 mg to about 16 mg of racemic reboxetine per unit dose which could be administered, for example 1 to 3 times per day. Another exemplary daily dose of the norepinephrine reuptake inhibitor is from about 1 mg to about 15 mg of [S,S]-reboxetine, preferably from about 2 mg to about 8 mg of [S,S]-reboxetine per unit dose which could be administered, for example 1 to 3 times per day. Another exemplary daily dose of the norepinephrine reuptake inhibitor is from about 150 mg to about 300 mg of amoxapine per unit dose, preferably between 200 mg and 275 mg of amoxapine per unit dose, which could be administered, for example 1 to 3 times per day. Another exemplary daily dose of the norepinephrine reuptake inhibitor is from about 25 mg to about 200 mg of maprotiline per unit dose, preferably between 50 mg and 150 mg of maprotiline per unit dose, which could be administered, for example 1 to 3 times per day.

An exemplary dose ratio by weight of a serotonin reuptake inhibitor to a norepinephrine reuptake inhibitor combination formulation for oral, parenteral or buccal administration to the average adult human for the treatment of the conditions referred to above is from about 0.00005 to about 20,000, preferably from about 0.25 to about 2,000.

In an exemplary embodiment of the invention, a serotonin reuptake inhibitor is present in a composition of the invention in an amount ranging from about 0.5% to about 90% by weight of the total composition, preferably from about 5% to about 80% by weight of the total composition; and a norepinephrine reuptake inhibitor is present in the composition of the invention in an amount ranging from about 0.5% to about 90% by weight of the total composition, preferably from about 5% to about 80% by weight of the total composition. The ratio by weight of the amount of the serotonin reuptake inhibitor to the amount of the norepinephrine reuptake inhibitor preferably ranges from 20:1 to 1:20, more preferably from 10:1 to 1:10.

Aerosol combination formulations for treatment of the conditions referred to above in a mammal, such as an average adult human are preferably arranged so that each metered

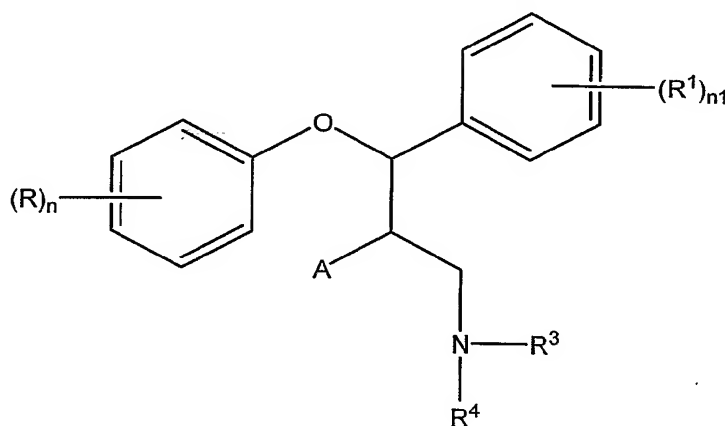
dose or "puff" of aerosol contains from about 100µg to about 30,000µg of the norepinephrine reuptake inhibitor, preferably from about 250µg to about 1,000µg of norepinephrine reuptake inhibitor, and from about 1,000µg to about 30,000µg of a serotonin reuptake inhibitor, preferably from about 5,000µg to about 20,000µg. Administration may be once or several
5 times daily, for example 1, 3, 4 or 8 times, giving for example, 1, 2 or 3 doses each time.

It should be understood that the present invention is not limited to the embodiments described herein. Numerous modifications can be made by one skilled in the art having the benefits of the teachings given here. Such modifications should be taken as being encompassed within the scope of the present invention as set forth in the appended claims.

What is claimed is:

1. A method for treating a disorder or condition that can be treated by enhancing serotonergic neurotransmission in a mammal, noradrenergic neurotransmission in a mammal, or a combination thereof, comprising administering to a mammal in need of such treatment: (i) at least one serotonin reuptake inhibitor or pharmaceutically acceptable salt thereof which is present in an amount sufficient for dopamine reuptake inhibition; and (ii) at least one norepinephrine reuptake inhibitor or pharmaceutically acceptable salt thereof, wherein the norepinephrine reuptake inhibitor is selected from the group consisting of:

(A) a compound having the formula of Structure II



Structure II

10

wherein n and n₁ are, independently, 1, 2 or 3; each of the groups R and R¹, which may be the same or different, is hydrogen; halogen; halo-C₁-C₆ alkyl; hydroxy; C₁-C₆ alkoxy; C₁-C₆ alkyl optionally substituted with C₁-C₆ alkyl or halogen; aryl- C₁-C₆ alkyl optionally substituted with C₁-C₆ alkyl or halogen; aryl- C₁-C₆ alkoxy optionally substituted with C₁-C₆ alkyl or halogen; --NO₂; -NR⁵R⁶ wherein R⁵ and R⁶ are, independently, hydrogen or C₁-C₆ alkyl, or two adjacent R groups or two adjacent R¹ groups, taken together, form the --O--CH₂--O-- group;

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A is H or OR²;

R² is hydrogen; C₁-C₁₂ alkyl optionally substituted with C₁-C₆ alkyl or halogen, or aryl-C₁-C₆ alkyl;

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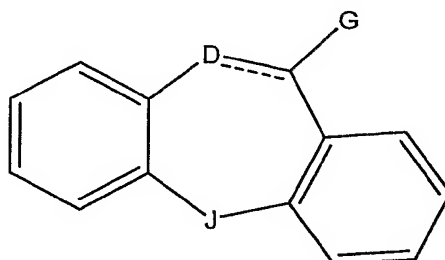
each of the groups R³ and R⁴, which may be identical or different, is hydrogen, C₁-C₆ alkyl optionally substituted with C₁-C₆ alkyl or halogen, C₂-C₄ alkenyl, C₂-C₄ alkynyl, aryl-C₁-C₄ alkyl optionally substituted with C₁-C₆ alkyl or halogen, C₃-C₇ cycloalkyl optionally substituted with C₁-C₆ alkyl or halogen, or R³ and R⁴ with the nitrogen atom to which they are bound form a pentatomic or hexatomic saturated or unsaturated, optionally substituted with C₁-C₆ alkyl or halogen, heteromonocyclic group optionally containing other heteroatoms selected from the group consisting of O, S and N;

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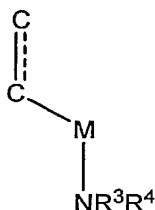
or R^2 and R^4 , taken together, form the $-\text{CH}_2-\text{CH}_2-$ group;

(B) a compound having the formula of Structure III



Structure III

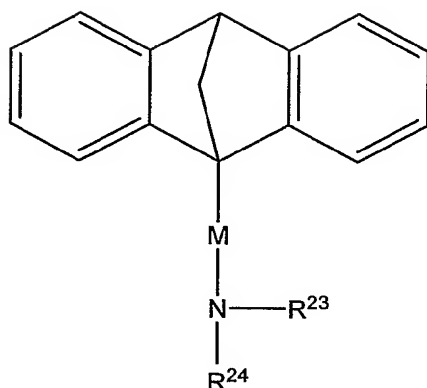
- wherein D is N or CR^9 , where R^9 is hydrogen, $\text{C}_1\text{-C}_6$ alkyl optionally substituted with $\text{C}_1\text{-C}_6$ alkyl or halogen, $\text{C}_2\text{-C}_4$ alkenyl, $\text{C}_2\text{-C}_4$ alkynyl, aryl- $\text{C}_1\text{-C}_4$ alkyl optionally substituted with $\text{C}_1\text{-C}_6$ alkyl or halogen, or $\text{C}_3\text{-C}_7$ cycloalkyl optionally substituted with $\text{C}_1\text{-C}_6$ alkyl or halogen; G is NR^7R^8 , wherein each of R^7 and R^8 is independently hydrogen, $\text{C}_1\text{-C}_6$ alkyl optionally substituted with $\text{C}_1\text{-C}_6$ alkyl or halogen, $\text{C}_2\text{-C}_4$ alkenyl, $\text{C}_2\text{-C}_4$ alkynyl, aryl- $\text{C}_1\text{-C}_4$ alkyl optionally substituted with $\text{C}_1\text{-C}_6$ alkyl or halogen, or $\text{C}_3\text{-C}_7$ cycloalkyl optionally substituted with $\text{C}_1\text{-C}_6$ alkyl or halogen; or R^7 and R^8 taken together with the nitrogen atom to which they are bound form a pentatomic or hexatomic, saturated or unsaturated, optionally substituted with $\text{C}_1\text{-C}_6$ alkyl or halogen heteromonocyclic group optionally containing one or more further additional heteroatoms selected from the group consisting of O, S and N; the bond between D and the ring carbon bonded to G is single or double; and J is O or L, where L is



- where the bond between the ring carbon of L and the carbon of L bonded to M is single or double; M is a C_n alkylene chain, where n is between 1 and 3; and each of R^{13} and R^{14} is independently hydrogen, $\text{C}_1\text{-C}_6$ alkyl optionally substituted with $\text{C}_1\text{-C}_6$ alkyl or halogen, $\text{C}_2\text{-C}_4$ alkenyl, $\text{C}_2\text{-C}_4$ alkynyl, aryl- $\text{C}_1\text{-C}_4$ alkyl optionally substituted with $\text{C}_1\text{-C}_6$ alkyl or halogen, $\text{C}_3\text{-C}_7$ cycloalkyl optionally substituted with $\text{C}_1\text{-C}_6$ alkyl or halogen, or R^{13} and R^{14} taken together with the nitrogen atom to which they are bound form a pentatomic or hexatomic, saturated or unsaturated, optionally substituted with $\text{C}_1\text{-C}_6$ alkyl or halogen heteromonocyclic group optionally containing one or more further additional heteroatoms selected from the group consisting of O, S and N; and

(C) a compound having the formula of Structure IV:

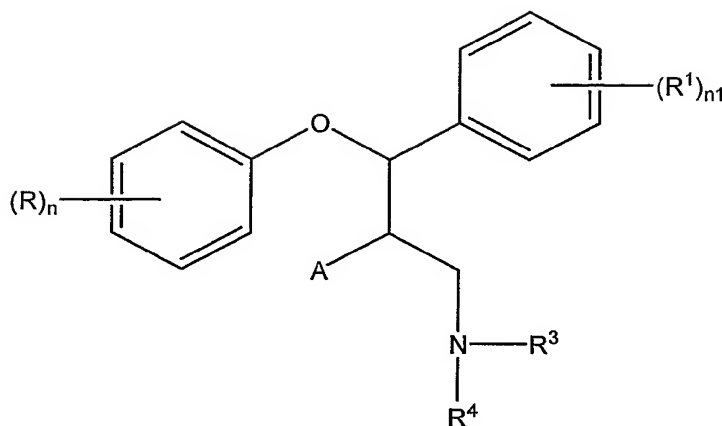
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Structure IV

- wherein M is a C_n alkylene chain, where n is between 1 and 3; and each of R²³ and R²⁴ is independently hydrogen, C₁-C₆ alkyl optionally substituted with C₁-C₆ alkyl or halogen, C₂-C₄ alkenyl, C₂-C₄ alkynyl, aryl-C₁-C₄ alkyl optionally substituted with C₁-C₆ alkyl or halogen, C₃-C₇ cycloalkyl optionally substituted with C₁-C₆ alkyl or halogen, or R²³ and R²⁴ taken together with the nitrogen atom to which they are bound form a pentatomic or hexatomic, saturated or unsaturated, optionally substituted with C₁-C₆ alkyl or halogen heteromonocyclic group optionally containing one or more further additional heteroatoms selected from the group consisting of O, S and N.
2. A method for treating depression in a mammal, comprising administering to a mammal in need of such treatment: (i) at least one serotonin reuptake inhibitor or pharmaceutically acceptable salt thereof which is present in an amount sufficient for dopamine reuptake inhibition; and (ii) at least one norepinephrine reuptake inhibitor or pharmaceutically acceptable salt thereof, wherein the norepinephrine reuptake inhibitor is selected from the group wherein the at least one norepinephrine reuptake inhibitor is selected from the group consisting of:
- (A) a compound having the formula of Structure II

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Structure II

wherein n and n_1 are, independently, 1, 2 or 3; each of the groups R and R^1 , which may be the same or different, is hydrogen; halogen; halo- C_1 - C_6 alkyl; hydroxy; C_1 - C_6 alkoxy; C_1 - C_6 alkyl optionally substituted with C_1 - C_6 alkyl or halogen; aryl- C_1 - C_6 alkyl optionally substituted with C_1 - C_6 alkyl or halogen; aryl- C_1 - C_6 alkoxy optionally substituted with C_1 - C_6 alkyl or halogen; $-\text{NO}_2$; $-\text{NR}^5\text{R}^6$ wherein R^5 and R^6 are, independently, hydrogen or C_1 - C_6 alkyl, or two adjacent R groups or two adjacent R^1 groups, taken together, form the $-\text{O}-\text{CH}_2-\text{O}-$ group;

A is H or OR^2 ;

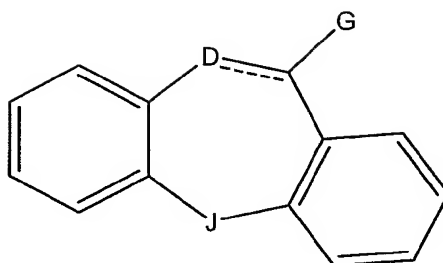
R^2 is hydrogen; C_1 - C_{12} alkyl optionally substituted with C_1 - C_6 alkyl or halogen, or aryl- C_1 - C_6 alkyl;

each of the groups R^3 and R^4 , which may be identical or different, is hydrogen, C_1 - C_6 alkyl optionally substituted with C_1 - C_6 alkyl or halogen, C_2 - C_4 alkenyl, C_2 - C_4 alkynyl, aryl- C_1 - C_4 alkyl optionally substituted with C_1 - C_6 alkyl or halogen, C_3 - C_7 cycloalkyl optionally substituted with C_1 - C_6 alkyl or halogen, or R^3 and R^4 with the nitrogen atom to which they are bound form a pentatomic or hexatomic saturated or unsaturated, optionally substituted with C_1 - C_6 alkyl or halogen, heteromonocyclic group optionally containing other heteroatoms selected from the group consisting of O , S and N ;

or R^2 and R^4 , taken together, form the $-\text{CH}_2-\text{CH}_2-$ group;

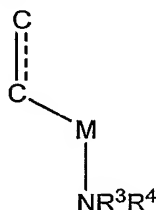
(B) a compound having the formula of Structure III

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Structure III

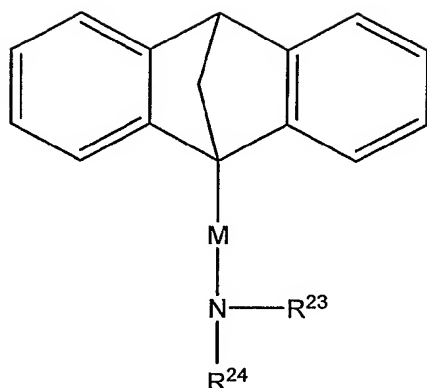
- wherein D is N or CR⁹, where R⁹ is hydrogen, C₁-C₆ alkyl optionally substituted with C₁-C₆ alkyl or halogen, C₂-C₄ alkenyl, C₂-C₄ alkynyl, aryl-C₁-C₄ alkyl optionally substituted with C₁-C₆ alkyl or halogen, or C₃-C₇ cycloalkyl optionally substituted with C₁-C₆ alkyl or halogen; G is
- 5 NR⁷R⁸, wherein each of R⁷ and R⁸ is independently hydrogen, C₁-C₆ alkyl optionally substituted with C₁-C₆ alkyl or halogen, C₂-C₄ alkenyl, C₂-C₄ alkynyl, aryl-C₁-C₄ alkyl optionally substituted with C₁-C₆ alkyl or halogen, or C₃-C₇ cycloalkyl optionally substituted with C₁-C₆ alkyl or halogen; or R⁷ and R⁸ taken together with the nitrogen atom to which they are bound form a pentatomic or hexatomic, saturated or unsaturated, optionally substituted
- 10 with C₁-C₆ alkyl or halogen heteromonocyclic group optionally containing one or more further additional heteroatoms selected from the group consisting of O, S and N; the bond between D and the ring carbon bonded to G is single or double; and J is O or L, where L is



- where the bond between the ring carbon of L and the carbon of L bonded to M is single or
- 15 double; M is a C_n alkylene chain, where n is between 1 and 3; and each of R¹³ and R¹⁴ is independently hydrogen, C₁-C₆ alkyl optionally substituted with C₁-C₆ alkyl or halogen, C₂-C₄ alkenyl, C₂-C₄ alkynyl, aryl-C₁-C₄ alkyl optionally substituted with C₁-C₆ alkyl or halogen, C₃-C₇ cycloalkyl optionally substituted with C₁-C₆ alkyl or halogen, or R¹³ and R¹⁴ taken together with the nitrogen atom to which they are bound form a pentatomic or hexatomic, saturated or
- 20 unsaturated, optionally substituted with C₁-C₆ alkyl or halogen heteromonocyclic group optionally containing one or more further additional heteroatoms selected from the group consisting of O, S and N; and

(C) a compound having the formula of Structure IV:

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Structure IV

wherein M is a C_n alkylene chain, where n is between 1 and 3; and each of R²³ and R²⁴ is independently hydrogen, C₁-C₆ alkyl optionally substituted with C₁-C₆ alkyl or halogen, C₂-C₄ alkenyl, C₂-C₄ alkynyl, aryl-C₁-C₄ alkyl optionally substituted with C₁-C₆ alkyl or halogen, C₃-C₇ cycloalkyl optionally substituted with C₁-C₆ alkyl or halogen, or R²³ and R²⁴ taken together with the nitrogen atom to which they are bound form a pentatomic or hexatomic, saturated or unsaturated, optionally substituted with C₁-C₆ alkyl or halogen heteromonocyclic group optionally containing one or more further additional heteroatoms selected from the group consisting of O, S and N.

3. The method of claim 2, wherein the disorder or condition is depression selected from the group consisting of depression in Parkinson's patients, Postmyocardial Infarction depression, depression in patients with human immunodeficiency virus (HIV), Subsyndromal Symptomatic depression, depression in infertile women, pediatric depression, major depression, single episode depression, recurrent depression, child abuse induced depression, post partum depression, DSM-IV major depression, treatment-refractory major depression, severe depression, psychotic depression, post-stroke depression, neuropathic pain, manic depressive illness, manic depressive illness with mixed episodes, manic depressive illness with depressive episodes, bipolar depression BP I, and bipolar depression BP II, melancholy, and major depression with dysthymia.

4. The method of claim 2, wherein the serotonin reuptake inhibitor is sertraline which is present in an amount sufficient for dopamine reuptake inhibition.

5. The method of claim 2, wherein the norepinephrine reuptake inhibitor or pharmaceutically acceptable salt thereof is present in an amount such that all norepinephrine transporters have an occupancy of at least 50% and the serotonin reuptake inhibitor or pharmaceutically acceptable salt thereof is present in an amount sufficient to displace at least about 45% β-CIT from the serotonin transporter as assessed by SPECT imaging.

6. The method of claim 2, wherein the norepinephrine reuptake inhibitor or pharmaceutically acceptable salt thereof is present in an amount such that all norepinephrine transporters have an occupancy of at least 75%.

7. The method of claim 2, wherein the serotonin reuptake inhibitor and the norepinephrine reuptake inhibitor are administered together in a pharmaceutical composition.

8. The method of claim 2, wherein the norepinephrine reuptake inhibitor is [S,S]-reboxetine administered in one or more unit doses each comprising about 1 to about 15 mg of [S,S]-reboxetine.

9. The method of claim 2, wherein the norepinephrine reuptake inhibitor is racemic reboxetine administered in one or more unit doses each comprising about 1 to about 30 mg of racemic reboxetine.

10. The method of claim 2, wherein the serotonin reuptake inhibitor is sertraline or a pharmaceutically acceptable salt thereof; the norepinephrine reuptake inhibitor is [S,S]-reboxetine or a pharmaceutically acceptable salt thereof, wherein sertraline is present in an amount sufficient for dopamine reuptake inhibition, wherein the amount of sertraline is from about 150 mg to about 200 mg.

11. A method for treating a disorder or condition for treating a disorder or condition selected from the group consisting of neuropathic pain, chronic pain, urinary incontinence, post-traumatic stress disorder, chronic stress, acute stress, fibromyalgia, depression comorbid with fibromyalgia, obesity, migraine, neuropathic pain associated with diabetes, affective symptoms of schizophrenia and a combination thereof in a mammal, the method comprising administering to a mammal in need of such treatment (i) at least one serotonin reuptake inhibitor or pharmaceutically acceptable salt thereof, wherein the at least one serotonin reuptake inhibitor is selected from the group consisting of sertraline, fluoxetine and fluvoxamine; and (ii) at least one norepinephrine reuptake inhibitor or pharmaceutically acceptable salt thereof, wherein the at least one norepinephrine reuptake inhibitor is selected from the group consisting of racemic reboxetine, [S,S]-reboxetine, amoxapine, and maprotiline.

12. The method of claim 11, wherein the serotonin reuptake inhibitor is sertraline which is present in an amount sufficient for dopamine reuptake inhibition.

13. A composition consisting essentially of (i) at least one serotonin reuptake inhibitor or pharmaceutically acceptable salt thereof, wherein the at least one serotonin reuptake inhibitor is sertraline which is present in an amount sufficient for dopamine reuptake inhibition; and (ii) at least one norepinephrine reuptake inhibitor or pharmaceutically acceptable salt thereof, wherein the at least one norepinephrine reuptake inhibitor is [S,S]-reboxetine.

14. A composition comprising sertraline or a pharmaceutically acceptable salt thereof and optionally a norepinephrine reuptake inhibitor selected from the group consisting of [S,S]-reboxetine, or pharmaceutically acceptable salts thereof, wherein sertraline or a

pharmaceutically acceptable salt thereof is present in an amount sufficient for dopamine reuptake inhibition.

15. The composition of claim 14, wherein sertraline is used in an amount ranging from about 150 mg to about 350 mg.

AMENDED CLAIMS

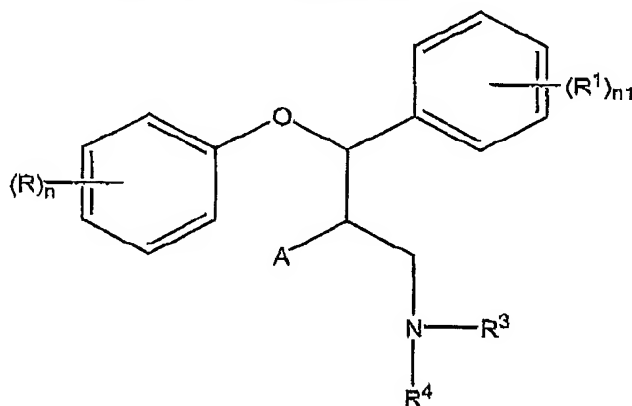
[received by the International Bureau on 04 February 2005 (04.02.2005);
original claims 1-15 replaced by new claims 1-23 (8 pages)]

+ STATEMENT

What is claimed is:

1. A method for treating a disorder or condition that can be treated by enhancing serotonergic neurotransmission in a mammal, noradrenergic neurotransmission in a mammal, or a combination thereof, comprising administering to a mammal in need of such treatment: (i) at least one serotonin reuptake inhibitor or pharmaceutically acceptable salt thereof wherein the serotonin reuptake inhibitor or pharmaceutically acceptable salt thereof is administered in an amount sufficient for dopamine reuptake inhibition; and (ii) at least one norepinephrine reuptake inhibitor or pharmaceutically acceptable salt thereof, wherein the norepinephrine reuptake inhibitor or pharmaceutically acceptable salt thereof is selected from the group consisting of:

(A) a compound having the formula of Structure II



Structure II

wherein n and n_1 are, independently, 1, 2 or 3; each or the groups R and R^1 , which may be the same or different, is hydrogen; halogen; halo- C_1-C_6 alkyl; hydroxy; C_1-C_6 alkoxy; C_1-C_6 alkyl optionally substituted with C_1-C_6 alkyl or halogen; aryl- C_1-C_6 alkyl optionally substituted with C_1-C_6 alkyl or halogen; aryl- C_1-C_6 alkoxy optionally substituted with C_1-C_6 alkyl or halogen; $-NO_2$; $-NR^5R^6$ wherein R^5 and R^6 are, independently, hydrogen or C_1-C_6 alkyl, or two adjacent R groups or two adjacent R^1 groups, taken together, form the $--O--CH_2--O--$ group;

A is H or OR^2 ;

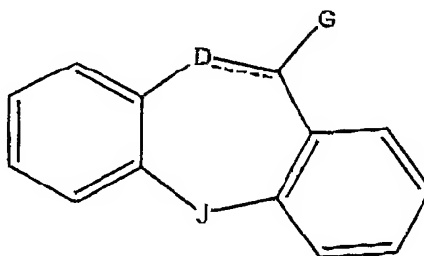
R^2 is hydrogen; C_1-C_{12} alkyl optionally substituted with C_1-C_6 alkyl or halogen, or aryl- C_1-C_6 alkyl;

each of the groups R^3 and R^4 , which may be identical or different, is hydrogen, C_1-C_6 alkyl optionally substituted with C_1-C_6 alkyl or halogen, C_2-C_4 alkenyl, C_2-C_4 alkynyl, aryl- C_1-C_4 alkyl optionally substituted with C_1-C_6 alkyl or halogen, C_3-C_7 cycloalkyl optionally substituted with C_1-C_6 alkyl or halogen, or R^3 and R^4 with the nitrogen atom to which they are bound form a pentatomic or hexatomic saturated or unsaturated, optionally substituted with C_1-C_6 alkyl or halogen, heteromonocyclic group optionally containing other heteroatoms selected from the group consisting of O, S and N;

or R^2 and R^4 , taken together, form the $-\text{CH}_2-\text{CH}_2-$ group;

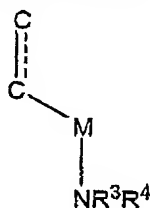
provided that the compound having the formula of Structure II is not racemic reboxetine or a pharmaceutically acceptable salt thereof;

(B) a compound having the formula of Structure III



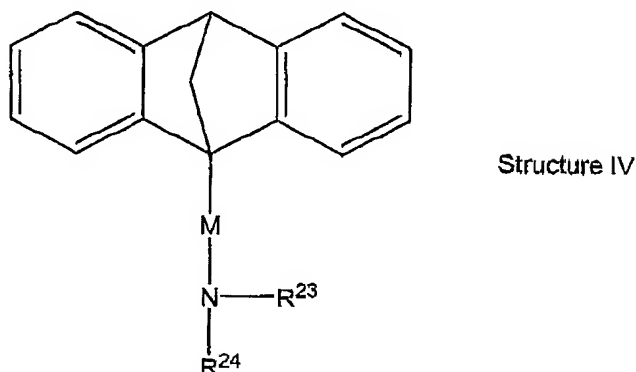
Structure III

wherein D is N or CR^9 , where R^9 is hydrogen, $\text{C}_1\text{-C}_6$ alkyl optionally substituted with $\text{C}_1\text{-C}_6$ alkyl or halogen, $\text{C}_2\text{-C}_4$ alkenyl, $\text{C}_2\text{-C}_4$ alkynyl, aryl- $\text{C}_1\text{-C}_4$ alkyl optionally substituted with $\text{C}_1\text{-C}_6$ alkyl or halogen, or $\text{C}_3\text{-C}_7$ cycloalkyl optionally substituted with $\text{C}_1\text{-C}_6$ alkyl or halogen; G is NR^7R^8 , wherein each of R^7 and R^8 is independently hydrogen, $\text{C}_1\text{-C}_6$ alkyl optionally substituted with $\text{C}_1\text{-C}_6$ alkyl or halogen, $\text{C}_2\text{-C}_4$ alkenyl, $\text{C}_2\text{-C}_4$ alkynyl, aryl- $\text{C}_1\text{-C}_4$ alkyl optionally substituted with $\text{C}_1\text{-C}_6$ alkyl or halogen, or $\text{C}_3\text{-C}_7$ cycloalkyl optionally substituted with $\text{C}_1\text{-C}_6$ alkyl or halogen; or R^7 and R^8 taken together with the nitrogen atom to which they are bound form a pentatomic or hexatomic, saturated or unsaturated, optionally substituted with $\text{C}_1\text{-C}_6$ alkyl or halogen heteromonocyclic group optionally containing one or more further additional heteroatoms selected from the group consisting of O, S and N; the bond between D and the ring carbon bonded to G is single or double; and J is O or L, where L is



where the bond between the ring carbon of L and the carbon of L bonded to M is single or double; M is a C_n alkylene chain, where n is between 1 and 3; and each of R^{13} and R^{14} is independently hydrogen, $\text{C}_1\text{-C}_6$ alkyl optionally substituted with $\text{C}_1\text{-C}_6$ alkyl or halogen, $\text{C}_2\text{-C}_4$ alkenyl, $\text{C}_2\text{-C}_4$ alkynyl, aryl- $\text{C}_1\text{-C}_4$ alkyl optionally substituted with $\text{C}_1\text{-C}_6$ alkyl or halogen, $\text{C}_3\text{-C}_7$ cycloalkyl optionally substituted with $\text{C}_1\text{-C}_6$ alkyl or halogen, or R^{13} and R^{14} taken together with the nitrogen atom to which they are bound form a pentatomic or hexatomic, saturated or unsaturated, optionally substituted with $\text{C}_1\text{-C}_6$ alkyl or halogen heteromonocyclic group optionally containing one or more further additional heteroatoms selected from the group consisting of O, S and N; and

(C) a compound having the formula of Structure IV:

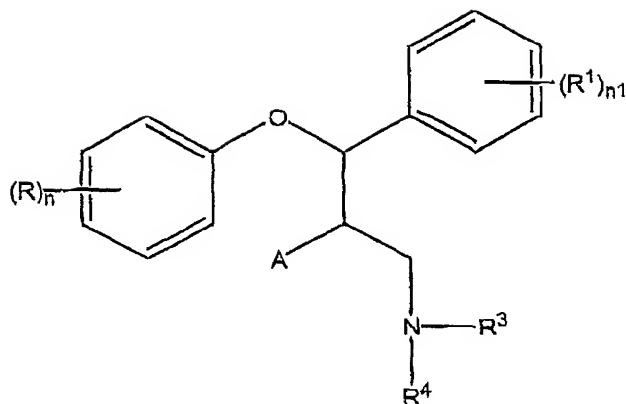


wherein M is a C_n alkylene chain, where n is between 1 and 3; and each of R^{23} and R^{24} is independently hydrogen, C_1 - C_6 alkyl optionally substituted with C_1 - C_6 alkyl or halogen, C_2 - C_4 alkenyl, C_2 - C_4 alkynyl, aryl- C_1 - C_4 alkyl optionally substituted with C_1 - C_6 alkyl or halogen, C_3 - C_7 cycloalkyl optionally substituted with C_1 - C_6 alkyl or halogen, or R^{23} and R^{24} taken together with the nitrogen atom to which they are bound form a pentatomic or hexatomic, saturated or unsaturated, optionally substituted with C_1 - C_6 alkyl or halogen heteromonocyclic group optionally containing one or more further additional heteroatoms selected from the group consisting of O, S and N.

2. A method for treating a disorder or condition that can be treated by enhancing serotonergic neurotransmission in a mammal, noradrenergic neurotransmission in a mammal, or a combination thereof, comprising administering to a mammal in need of such treatment: (i) at least one serotonin reuptake inhibitor or pharmaceutically acceptable salt thereof wherein the serotonin reuptake inhibitor or pharmaceutically acceptable salt thereof is administered in an amount sufficient for dopamine reuptake inhibition; and (ii) at least one norepinephrine reuptake inhibitor or pharmaceutically acceptable salt thereof, wherein the norepinephrine reuptake inhibitor or pharmaceutically acceptable salt thereof is [S,S]-reboxetine or a pharmaceutically acceptable salt thereof.

3. A method for treating depression in a mammal, comprising administering to a mammal in need of such treatment: (i) at least one serotonin reuptake inhibitor or pharmaceutically acceptable salt thereof wherein the serotonin reuptake inhibitor or pharmaceutically acceptable salt thereof is administered in an amount sufficient for dopamine reuptake inhibition; and (ii) at least one norepinephrine reuptake inhibitor or pharmaceutically acceptable salt thereof, wherein the norepinephrine reuptake inhibitor or pharmaceutically acceptable salt thereof is selected from the group consisting of:

(A) a compound having the formula of Structure II



Structure II

wherein n and n_1 are, independently, 1, 2 or 3; each of the groups R and R^1 , which may be the same or different, is hydrogen; halogen; halo- C_1-C_6 alkyl; hydroxy; C_1-C_6 alkoxy; C_1-C_6 alkyl optionally substituted with C_1-C_6 alkyl or halogen; aryl- C_1-C_6 alkyl optionally substituted with C_1-C_6 alkyl or halogen; aryl- C_1-C_6 alkoxy optionally substituted with C_1-C_6 alkyl or halogen; $-NO_2$; $-NR^5R^6$ wherein R^5 and R^6 are, independently, hydrogen or C_1-C_6 alkyl, or two adjacent R groups or two adjacent R^1 groups, taken together, form the $-O-CH_2-O-$ group;

A is H or OR^2 ;

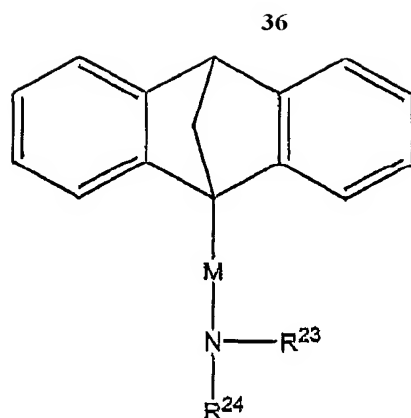
R^2 is hydrogen; C_1-C_{12} alkyl optionally substituted with C_1-C_6 alkyl or halogen, or aryl- C_1-C_6 alkyl;

each of the groups R^3 and R^4 , which may be identical or different, is hydrogen, C_1-C_6 alkyl optionally substituted with C_1-C_6 alkyl or halogen, C_2-C_4 alkenyl, C_2-C_4 alkynyl, aryl- C_1-C_4 alkyl optionally substituted with C_1-C_6 alkyl or halogen, C_3-C_7 cycloalkyl optionally substituted with C_1-C_6 alkyl or halogen, or R^3 and R^4 with the nitrogen atom to which they are bound form a pentatomic or hexatomic saturated or unsaturated, optionally substituted with C_1-C_6 alkyl or halogen, heteromonocyclic group optionally containing other heteroatoms selected from the group consisting of O, S and N;

or R^2 and R^4 , taken together, form the $-CH_2-CH_2-$ group;

provided that the compound having the formula of Structure II is not racemic reboxetine or a pharmaceutically acceptable salt thereof;

(B) a compound having the formula of Structure III



wherein M is a C_n alkylene chain, where n is between 1 and 3; and each of R^{23} and R^{24} is independently hydrogen, C_1 - C_6 alkyl optionally substituted with C_1 - C_6 alkyl or halogen, C_2 - C_4 alkenyl, C_2 - C_4 alkynyl, aryl- C_1 - C_4 alkyl optionally substituted with C_1 - C_6 alkyl or halogen, C_3 - C_7 cycloalkyl optionally substituted with C_1 - C_6 alkyl or halogen, or R^{23} and R^{24} taken together with the nitrogen atom to which they are bound form a pentatomic or hexatomic, saturated or unsaturated, optionally substituted with C_1 - C_6 alkyl or halogen heteromonocyclic group optionally containing one or more further additional heteroatoms selected from the group consisting of O, S and N.

4. A method for treating depression in a mammal, comprising administering to a mammal in need of such treatment: (i) at least one serotonin reuptake inhibitor or pharmaceutically acceptable salt thereof wherein the serotonin reuptake inhibitor or pharmaceutically acceptable salt thereof is administered in an amount sufficient for dopamine reuptake inhibition; and (ii) at least one norepinephrine reuptake inhibitor or pharmaceutically acceptable salt thereof, wherein the norepinephrine reuptake inhibitor or pharmaceutically acceptable salt thereof is [S,S]-reboxetine or a pharmaceutically acceptable salt thereof.

5. The method of claim 3 or claim 4, wherein the depression is selected from the group consisting of depression in Parkinson's patients, Postmyocardial Infarction depression, depression in patients with human immunodeficiency virus (HIV), Subsyndromal Symptomatic depression, depression in infertile women, pediatric depression, major depression, single episode depression, recurrent depression, child abuse induced depression, post partum depression, DSM-IV major depression, treatment-refractory major depression, severe depression, psychotic depression, post-stroke depression, neuropathic pain, manic depressive illness, manic depressive illness with mixed episodes, manic depressive illness with depressive episodes, bipolar depression BP I, and bipolar depression BP II, melancholy, and major depression with dysthymia.

6. The method of claim 3 or claim 4, wherein the serotonin reuptake inhibitor or a pharmaceutically acceptable salt thereof is sertraline or a pharmaceutically acceptable salt thereof.

7. The method of claim 6, wherein the serotonin reuptake inhibitor is a chloride salt of sertraline.

8. The method of claim 3 or claim 4, wherein the norepinephrine reuptake inhibitor or pharmaceutically acceptable salt thereof is administered in an amount sufficient to achieve at least 50% occupancy of all norepinephrine transporters and the serotonin reuptake inhibitor or pharmaceutically acceptable salt thereof is administered in an amount sufficient to displace at least about 45% β -CIT from a serotonin transporter as assessed by SPECT imaging.

9. The method of claim 3 or claim 4, wherein the norepinephrine reuptake inhibitor or pharmaceutically acceptable salt thereof is administered in an amount sufficient to achieve at least 75% occupancy of all norepinephrine transporters.

10. The method of claim 3 or claim 4, wherein the serotonin reuptake inhibitor or a pharmaceutically acceptable salt thereof and the norepinephrine reuptake inhibitor or a pharmaceutically acceptable salt thereof are administered within the same pharmaceutical composition.

11. The method of claim 4, wherein the [S,S]-reboxetine or a pharmaceutically acceptable salt thereof is administered in one or more unit doses each comprising about 1 to about 15 mg of [S,S]-reboxetine.

12. The method of claim 4, wherein the [S,S]-reboxetine or a pharmaceutically acceptable salt thereof is administered in one or more unit doses each comprising about 1 to about 30 mg of [S,S]-reboxetine.

13. The method of claim 4, wherein the serotonin reuptake inhibitor or a pharmaceutically acceptable salt thereof is sertraline or a pharmaceutically acceptable salt thereof; and wherein the amount of sertraline is from about 150 mg to about 200 mg.

14. A method for treating a disorder or condition selected from the group consisting of neuropathic pain, chronic pain, urinary incontinence, post-traumatic stress disorder, chronic stress, acute stress, fibromyalgia, depression comorbid with fibromyalgia, obesity, migraine, neuropathic pain associated with diabetes, affective symptoms of schizophrenia and a combination thereof in a mammal, the method comprising administering to a mammal in need of such treatment (i) at least one serotonin reuptake inhibitor or pharmaceutically acceptable salt thereof, wherein the at least one serotonin reuptake inhibitor or a pharmaceutically acceptable salt thereof is selected from the group consisting of sertraline, fluoxetine and fluvoxamine, or a pharmaceutically acceptable salt thereof; and (ii) at least one norepinephrine reuptake inhibitor or pharmaceutically acceptable salt thereof, wherein the at least one norepinephrine reuptake inhibitor or a pharmaceutically acceptable salt thereof is selected from the group consisting of racemic reboxetine, [S,S]-reboxetine, amoxapine, and maprotiline, or a pharmaceutically acceptable salt thereof.

15. The method of claim 14, wherein the serotonin reuptake inhibitor is sertraline or a pharmaceutically acceptable salt thereof.

16. A composition consisting essentially of (i) at least one serotonin reuptake inhibitor or pharmaceutically acceptable salt thereof, wherein the at least one serotonin reuptake inhibitor is sertraline

or a pharmaceutically acceptable salt thereof which is present in an amount sufficient for dopamine reuptake inhibition; and (ii) at least one norepinephrine reuptake inhibitor or pharmaceutically acceptable salt thereof, wherein the at least one norepinephrine reuptake inhibitor is [S,S]-reboxetine or a pharmaceutically acceptable salt thereof.

17. A composition comprising sertraline or a pharmaceutically acceptable salt thereof, wherein sertraline or a pharmaceutically acceptable salt thereof is present in an amount sufficient for dopamine reuptake inhibition.

18. The composition of claim 17, further comprising a norepinephrine reuptake inhibitor or a pharmaceutically acceptable salt thereof, wherein the norepinephrine reuptake inhibitor or a pharmaceutically acceptable salt thereof is [S,S]-reboxetine or a pharmaceutically acceptable salt thereof.

19. The composition of claim 16, wherein the amount of sertraline ranges from about 150 mg to about 350 mg.

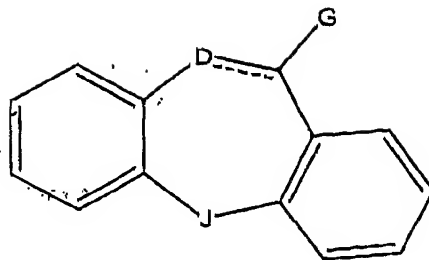
20. The composition of claim 17, wherein the amount of sertraline ranges from about 150 mg to about 350 mg.

21. The composition of claim 18, wherein the amount of sertraline ranges from about 150 mg to about 350 mg.

22. Use of a composition comprising at least one serotonin reuptake inhibitor or a pharmaceutically acceptable salt thereof and at least one norepinephrine reuptake inhibitor or a pharmaceutically acceptable salt thereof for preparing a medicament for treating depression.

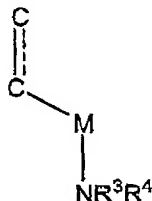
23. Use of a composition comprising at least one serotonin reuptake inhibitor or a pharmaceutically acceptable salt thereof, wherein the at least one serotonin reuptake inhibitor or a pharmaceutically acceptable salt thereof is present in an amount sufficient for dopamine reuptake inhibition, and at least one norepinephrine reuptake inhibitor or a pharmaceutically acceptable salt thereof for preparing a medicament for treating depression.

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Structure III

wherein D is N or CR⁹, where R⁹ is hydrogen, C₁-C₆ alkyl optionally substituted with C₁-C₆ alkyl or halogen, C₂-C₄ alkenyl, C₂-C₄ alkynyl, aryl-C₁-C₄ alkyl optionally substituted with C₁-C₆ alkyl or halogen, or C₃-C₇ cycloalkyl optionally substituted with C₁-C₆ alkyl or halogen; G is NR⁷R⁸, wherein each of R⁷ and R⁸ is independently hydrogen, C₁-C₆ alkyl optionally substituted with C₁-C₆ alkyl or halogen, C₂-C₄ alkenyl, C₂-C₄ alkynyl, aryl-C₁-C₄ alkyl optionally substituted with C₁-C₆ alkyl or halogen, or C₃-C₇ cycloalkyl optionally substituted with C₁-C₆ alkyl or halogen; or R⁷ and R⁸ taken together with the nitrogen atom to which they are bound form a pentatomic or hexatomic, saturated or unsaturated, optionally substituted with C₁-C₆ alkyl or halogen heteromonocyclic group optionally containing one or more further additional heteroatoms selected from the group consisting of O, S and N; the bond between D and the ring carbon bonded to G is single or double; and J is O or L, where L is



where the bond between the ring carbon of L and the carbon of L bonded to M is single or double; M is a C_n alkylene chain, where n is between 1 and 3; and each of R¹³ and R¹⁴ is independently hydrogen, C₁-C₆ alkyl optionally substituted with C₁-C₆ alkyl or halogen, C₂-C₄ alkenyl, C₂-C₄ alkynyl, aryl-C₁-C₄ alkyl optionally substituted with C₁-C₆ alkyl or halogen, C₃-C₇ cycloalkyl optionally substituted with C₁-C₆ alkyl or halogen, or R¹³ and R¹⁴ taken together with the nitrogen atom to which they are bound form a pentatomic or hexatomic, saturated or unsaturated, optionally substituted with C₁-C₆ alkyl or halogen heteromonocyclic group optionally containing one or more further additional heteroatoms selected from the group consisting of O, S and N; and

(C) a compound having the formula of Structure IV:

STATEMENT UNDER ARTICLE 19(1) (Rule 46.4)

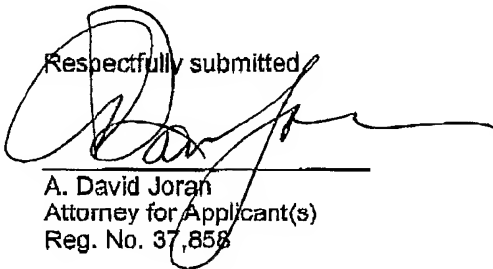
Applicant respectfully requests that the claims as filed be replaced with the appended amended claims on the replacement sheets. Applicant respectfully submits that former claims 1-15 have been amended without prejudice to applicant's right to prosecute any subject matter no longer being claimed. Claims 2, 4, 7, 18, and 20-23 have been added.

None of these amendments or new claims adds any new matter.

Applicant respectfully submits that amended claims 1-23 submitted herewith are fully supported by the description in accord with the requirements of Articles 5 and 6 of the Patent Cooperation Treaty. Applicant submits that the presently claimed subject matter meets the requirements of novelty, inventive step, and industrial applicability.

Date: February 8, 2005

Respectfully submitted



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INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB2004/002864

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/5375 A61K31/135 A61P25/24

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, EMBASE, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HARKIN ANDREW ET AL: "Activity and onset of action of reboxetine and effect of combination with sertraline in an animal model of depression" EUROPEAN JOURNAL OF PHARMACOLOGY, vol. 364, no. 2-3, 8 January 1999 (1999-01-08), pages 123-132, XP002306748 ISSN: 0014-2999 cited in the application abstract ----- -/--	1-15

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *G* document member of the same patent family

Date of the actual completion of the international search

22 November 2004

Date of mailing of the international search report

08/12/2004

Name and mailing address of the ISA

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Authorized officer

Young, A

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB2004/002864

G.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HARKIN A ET AL: "Effects of reboxetine and sertraline treatments alone and in combination on the binding properties of cortical NMDA and beta1-adrenergic receptors in an animal model of depression" JOURNAL OF NEURAL TRANSMISSION, vol. 107, no. 10, 25 October 2000 (2000-10-25), pages 1213-1227, XP002306749 ISSN: 0300-9564 cited in the application page 1220; figure 2 abstract -----	1-15
X	FERRI M ET AL: "Sertraline and Reboxetine association in depressive pseudodementia: Good cardiovascular effects." ARCHIVES OF GERONTOLOGY AND GERIATRICS SUPPLEMENT, vol. 7, 2001, pages 121-125, XP002306750 ISSN: 0924-7947 page 123, paragraph 5 -----	1-15
Y	HAUSER R A ET AL: "Sertraline for the treatment of depression in Parkinson's disease." MOVEMENT DISORDERS : OFFICIAL JOURNAL OF THE MOVEMENT DISORDER SOCIETY. SEP 1997, vol. 12, no. 5, September 1997 (1997-09), pages 756-759, XP009040237 ISSN: 0885-3185 page 756, right-hand column, lines 4-18 abstract -----	1-15
Y	SCHMITT JEROEN A J ET AL: "Non-serotonergic pharmacological profiles and associated cognitive effects of serotonin reuptake inhibitors" JOURNAL OF PSYCHOPHARMACOLOGY, vol. 15, no. 3, September 2001 (2001-09), pages 173-179, XP009040258 ISSN: 0269-8811 abstract -----	1-15
Y	SKOLNICK PHIL ET AL: "Antidepressant-like actions of DOV 21,947: A "triple" reuptake inhibitor." EUROPEAN JOURNAL OF PHARMACOLOGY, vol. 461, no. 2-3, 14 February 2003 (2003-02-14), pages 99-104, XP002306753 ISSN: 0014-2999 abstract ----- ----- -/--	1-15

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB2004/002864

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	DEMITRACK MARK A: "Can monoamine-based therapies be improved?" JOURNAL OF CLINICAL PSYCHIATRY, vol. 63, no. Supplement 2, 2002, pages 14-18, XP009040277 ISSN: 0160-6689 abstract	1-15
X,P	WO 03/090743 A (CYPRESS BIOSCIENCE INC) 6 November 2003 (2003-11-06) page 8, lines 9-11 page 9, line 28 - page 10, line 16 page 19, lines 14-21	1-15

INTERNATIONAL SEARCH REPORT

In International application No.
PCT/IB2004/002864

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: —
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 1-12 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB2004/002864

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 03090743	A	06-11-2003	WO 03090743 A1	06-11-2003
			US 2003232805 A1	18-12-2003